REMARKS

Status of the Application

Claims 1-5 were originally filed in this application. Claim 1 is amended to remove the quotation marks in part (e), claim 5 is cancelled, and claims 6-14 are added. Therefore, claims 1-4 and 6-14 are currently pending. The new claims are supported by the application as a whole. Claim 6 is supported, *inter alia*, in Figure 1A; at page 3, line 31, to page 3, line 4; at page 20, lines 1-24; and in Examples 5-7, at pages 34-37. Claim 7 is supported, among other locations, at page 5, lines 29-32, and at page 36, lines 2-5. Claims 8 and 9 are supported, among other locations, at page 5, lines 8-9, and in Example 1, at page 12, lines 17-22. Claim 10 is supported, *inter alia*, at page 7, lines 14-15, and in Example I, part III, at page 14, line 17, to page 15, line 11. Claims 11-13 are supported, inter alia, at page 5, line 29, to page 6, line 6, at page 11, lines 1-16, and in original claim 5.

Applicants also amend the specification to convert the term "BIAcore®" at pages 8, 9, 32, and 33 to U.S. Patent and Trademark Office format.

The above amendments and new claims do not introduce new matter into the application, or require a further search of the art. Applicants respectfully request their entry.

Objections to the Specification

The Office objects to the format of the trade-name BIAcore®. (Office Action at page 2.) The present amendments modify the format of this term wherever it is recited in the specification. Thus, Applicants respectfully request the withdrawal of this objection.

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The Office also asserts that biological deposit information is not provided for the antibodies listed in claim 5. (Office Action at page 2.) This objection is now moot, as claim 5 is canceled. Moreover, as noted in the following section, those antibodies are polyclonal antibodies obtained as described at page 11 of the specification, lines 1-16.

Rejection of Claim 5 Under 35 U.S.C. § 112, First Paragraph

The Office rejects this claim, asserting that, to the extent that the antibodies recited in claim 5 are monoclonal antibodies, the claim is not enabled without information as to the deposit of the antibodies. (Office Action at pages 2-3.) Applicants note that claim 5 is now canceled. The antibodies listed in claim 5 are polyclonal antibodies obtained as described in the specification at page 11, lines 1-16. Because one of ordinary skill can repeat this immunization with readily obtainable materials and routine procedures, Applicants submit that the claims are enabled.

Rejection of Claims 1 and 2 under 35 U.S.C. § 112, Second Paragraph

The Office rejects these claims, asserting that the term "derivative" renders them indefinite and unclear. (Office Action at pages 3-4.) Applicants respectfully traverse this rejection and submit that the meaning of the term "derivative" is clear.

Definiteness must be analyzed in light of the application's disclosure. M.P.E.P. § 2164.02. For example, the present specification refers to a number of "derivatives" of recombinant human insulin, such as "HIA1" Gly(A21)-Arg(B31)-Arg(B32)-human insulin, "HIA2" Lys-(B3)-Glu(B29)-human insulin, and their corresponding preproinsulins, C-peptides, and trypsin or endoproteinase cleavage products. (Specification, pages 2-3.) Preproinsulin "derivatives" and insulin "derivatives" of claims 1 and 2 include those

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peptides derived from the full length recombinant proteins as a result of enzymatic cleavage, such as with trypsin or carboxypeptidase. These include polypeptide fragments produced by correct, incorrect, and incomplete enzymatic cleavages, for example.

Thus, Applicants intend "derivative" to include human insulin products that are naturally produced during recombinant insulin production and, for example, products of later processing events, such as trypsin and endoproteinase cleavages, and various "model compounds" used as controls in the claimed assay. Figure 1A and the working examples depict a variety of such "derivatives." Applicants submit therefore, that one of ordinary skill in the art would understand the meaning of "derivative" as it is used in claims 1 and 2 because many example "derivatives" are discussed in the specification.

Moreover, to satisfy the requirements of § 112, second paragraph, only reasonable clarity, not exact precision, is required. M.P.E.P. § 2173.02; emphasis in original. So long as one of ordinary skill in the art, with the application to provide guidance, would understand the meaning of the terms used, the claims are definite. Because one of ordinary skill would understand the meaning of "derivative" in the present context, claims 1 and 2 are definite, and Applicants request that this rejection be withdrawn.

Rejection of Claims 1-3 under § 102(b)

The Office rejects claims 1-3, alleging that they are anticipated by Hara et al. ("Hara"; EP 0 484 961). (Office Action at pages 4-5.) Applicants respectfully traverse this rejection.

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The Office contends that Hara teaches measuring human C-peptide in a sample by contacting the sample with an antibody specific for C-peptide, a tracer C-peptide, and a labeled antibody for determining the immunoreaction products, citing claims 1-7 of Hara. The Office also contends that Hara inherently encompasses the claimed "recombinant human insulin or derivative thereof" even though it does not teach recombinant insulin.

Applicants note that for a reference to anticipate a claim under § 102(b), each and every element of that claim must be disclosed in the reference either expressly or inherently. M.P.E.P. § 2131. The identical invention must be shown in as complete detail as is recited in the claim. *Id.* In other words, if any element is missing or incomplete, there is no anticipation. *Id.* Applicants submit that Hara cannot anticipate the claimed invention because it does not teach each and every element of claim 1.

For example, the Office focuses upon the claims of Hara. However, the first four of Hara's claims do not include any C-peptide "tracer" element. Therefore, they lack step (c) of instant claim 1. Hara's remaining claims do not include any "C-peptide second antibody" at all, and thus lack step (e) of instant claim 1.

Hara's general disclosure suffers from the same deficiency. For example, in the "sandwich" assay described at page 2, lines 35-54, no labeled C-peptide tracer is used at all. Instead, the label is placed upon a secondary or tertiary antibody. In the second "competitive" assay described at page 3, lines 10-26, only the C-peptide is labeled, and no second antibody is used at all. Instead, only the labeled C-peptide is used in detection. For instance, in describing the competitive assay, Hara expressly states that "either the label of the unreacted labeled human C-peptide or the label of the

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immunoreaction product produced from the labeled human C-peptide is detected." (Hara at page 3, lines 16-18.) Hara's working examples at page 3, line 30, to page 4, line 48, demonstrate its "sandwich" assay in which no C-peptide tracer is used. In summary, Hara's "sandwich" assay lacks part (c) of instant claim 1, while its "competitive" assay lacks part (e) of instant claim 1.

Furthermore, Hara expressly points out that the "sandwich" assay and "competitive" assay are two *different* assays. For example, Hara calls each assay a separate method at several locations in the disclosure and claims each assay in a separate independent claim. (*See* Hara at Abstract, page 2, lines 23-33 and line 35, page 3, line 10, and claims 1 and 5.) Thus, in contrast to Applicants' claim 1, Hara does not suggest or imply any single assay in which both a C-peptide tracer and a C-peptide second antibody are used in the detection of a C-peptide impurity. In addition, nothing in Hara suggests placing a C-peptide second antibody on a bead, as Applicants claim.

Because Hara does not teach expressly or inherently any method comprising both of steps (c) and (e) of instant claims 1-3, it cannot anticipate these claims. For this reason, the Office's contention that Hara's method might inherently be capable of detecting recombinant human insulin or derivatives thereof need not be addressed. In light of these remarks, Applicants respectfully request the withdrawal of this rejection.

Rejection of Claim 4 under 35 U.S.C. § 103(a)

The Office rejects claim 4 as allegedly obvious over Hara, discussed above, in light of Campbell (Section 1.3.4, page 29, *Monoclonal Antibody Technology* (1984)) and Naithani et al. (Abstract from *Fed. Rep. Ger. Intl. Congress Ser.* 468: 94-98 (1979)).

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The Office contends that Hara teaches all of the elements of claim 1, but notes that Hara does not mention any anti-monkey-C-peptide antibody. The Office relies on Campbell and Naithani for motivation to prepare an anti-monkey-C-peptide antibody. Applicants also traverse this rejection, and submit that this combination does not present a *prima facie* case of obviousness because Hara does not teach or suggest all of the elements of claim 1, and because there is insufficient motivation to combine these three references, and no reasonable expectation of success in performing the combination.

There are three requirements for a *prima facie* case of obviousness. M.P.E.P. § 2143. First, the combination of references, as a whole, must teach or suggest all of the limitations of the claim. *Id.*; M.P.E.P. § 2143.03. Second, there must be a motivation or suggestion, either in the references themselves, or in the knowledge available to one of ordinary skill in the art, to combine the teachings of the references so as to produce the claimed invention. *Id.*; M.P.E.P. § 2143.01. Third, there must a reasonable expectation of success in performing the combination. *Id.*; M.P.E.P. § 2143.02.

Moreover, the motivation to combine the references and the reasonable expectation of success must both be found in the references themselves or in the knowledge generally available to one of ordinary skill in the art, and not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); M.P.E.P. § 2142. The mere fact that the references *can* be combined or modified does not itself render the combination obvious. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir.

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1990). The modification or combination must be *desirable*, not merely feasible. M.P.E.P. § 2143.01; *Winner v. Wang*, 53 U.S.P.Q.2d 1580, 1587-8 (Fed. Cir. 2000).

Applicants have described the teachings of Hara in the previous section, and note that Hara does not teach critical elements of instant claim 1, from which claim 4 depends. In short, Hara does not teach or suggest a method including both steps (c) and (e) of claim 1, in which both a C-peptide tracer and a labeled C-peptide second antibody bead are used together. Campbell and Naithani do not provide those missing elements. Naithani relates to the synthesis monkey-C-peptide derivatives for a radioimmunoassay. (See the accompanying Information Disclosure Statement for a complete copy of Naithani.) Campbell is an introductory book chapter that describes the properties and uses of antibodies in only very general terms. Therefore, the combination of Hara, Campbell, and Naithani does not teach or suggest all of the claim elements, and thereby fails the first requirement of a *prima facie* case of obviousness.

In addition, there is no motivation to combine the teachings of Hara, Campbell, and Naithani so as to generate the instant claimed invention. Thus, even if, *arguendo*, all of the claim elements were taught or suggested by the combined references, the combination would still fail to rise to the level of a *prima facie* case.

For example, Hara does not teach that it would be desirable to perform a non-radioactive sandwich or competition assay of recombinant insulin using both a C-peptide tracer and a second antibody bead carrying at least one label, as Applicants claim. Instead, Hara teaches that either a sandwich assay without any C-peptide tracer or a competitive assay without a second antibody achieves good detection of C-peptide in samples. Thus, Hara does not provide one of ordinary skill in the art with any desire

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to look beyond one of those two assays. Even if it is feasible to add other elements to one of Hara's assays, obviousness is based on what is *desirable*, not on what is merely feasible. M.P.E.P. § 2143.01; *Winner v. Wang*, 53 U.S.P.Q.2d 1580, 1587-8 (Fed. Cir. 2000). Thus, there is no motivation in Hara, or in Campbell or Naithani, to prepare the assay of either instant claim 1 or claim 4.

Finally, none of Hara, Campbell, or Naithani teaches the desirability of detecting C-peptide impurities in a recombinant insulin sample, or provides one of ordinary skill in the art with a reasonable expectation of success in combining their teachings to detect such impurities. Instead, Hara teaches the desirability of detecting isolated C-peptide as a marker for the concentration of cleaved insulin in the blood, for example in diagnosis and monitoring of diabetes. (*See* Hara at page 2, lines 1-9.) Hara implies that one should prepare an antibody that does not significantly cross-react with uncleaved, inactive preproinsulin. (*Id.*) However, as the instant specification points out, antibodies useful in the present invention should have a reasonable degree of affinity for preproinsulin as well as for derivatives caused by improper protease cleavages. (Specification at page 7, line 12, and page 20, lines 1-23.) Thus, if one were to combine the teachings of Hara with those of Campbell and Naithani, there would be no reasonable expectation of success in performing the claimed assay because one could not be certain that all of the major types of impurities could be detected.

To illustrate this point, Applicant's specification and figures that demonstrate that the claimed assay provides superior results in comparison to three prior art assays: two radioimmunoassays and an ELIZA sandwich assay. (See Example 2, at pages 21-28.) Hara's assay appears to be similar to the "NewLab Sandwich ELIZA" assay against

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which the claimed "bead" assay was tested. The specification at page 27, lines 8-18, describes some of the problems encountered with the NewLab assay. The NewLab assay gave generally variable, unsatisfactory, results compared to the claimed assay. (*Id.*) Further, because the NewLab assay is designed to detect only isolated C-peptide, it is not clear how well the NewLab antibodies recognize other impurities such as preproinsulin. (*Id.*) An assay based upon combining Hara with Campbell and Naithani would likely suffer from this same deficiency because, like the NewLab protocol, Hara teaches detecting solely isolated C-peptide. Thus, there would be no reasonable expectation of success in combining these three references.

Because the Office does not present a *prima facie* case of obviousness, Applicants request that the Office withdraw this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of claims 1-4 and 6-14.

Please grant any extensions of time required to enter this response and charge any required fees not submitted herewith to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: April 21, 2003

By: _____
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Filed: October 26, 2000

APPENDIX TO AMENDMENT OF APRIL 21, 2003

Version Showing Changes Marked-Up

IN THE SPECIFICATION:

Please amend the specification as follows:

Please replace the text at page 8, lines 24-25, with the following:

Sensor chips CM5, Pharmacia [BIAcore] BIACORE®

Carbodiimide coupling kit, Pharmacia [BIAcore] BIACORE®

Please replace the text at page 8, lines 24-25, with the following:

[BIAcore] BIACORE® 1000, Pharmacia [BIAcore] BIACORE®

Please replace the paragraph at page 32, lines 9-14, with the following:

Nonspecific sheep antibodies, as well as serum components, cannot interact with the affinity resin of the second column and thus, flow through the column into the eluate. Total capture of specific antibodies by the affinity column was checked by analysis of

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the flow-through making use of the [BIAcore®] BIACORE® system. In the flow-through fraction, there was no binding activity detectable.

Please replace the paragraph at page 32, lines 21-26, with the following:

Figure 4A depicts the elution profile of a human insulin chromatographed on an Azlacton HR 16/11 column. The elution profile of the PPI EMD Azlacton column is shown in Figure 4B. Fractions 9 –22 contain active anti-monkey insulin C-peptide antibodies as analyzed with the [BIAcore®] BIACORE® system. The indicated fractions were pooled and concentrated to 10 mL using Amicon Ultrafree-15 units (10 kDa molecular weight cut off membranes).

Please replace the paragraph at page 33, lines 3-8, with the following:

The flow-through of the affinity tandem column as well as the eluants of the PPI EMD Fractogel and Superdex 200 columns were analyzed using the [BIAcore®] BIACORE® system. This technique allows the fast detection of anti-monkey insulin C-peptide antibodies by simulation of the affinity chromatography in a 60 nL flow cell generated on the surface of a sensor chip. Active antibodies binding to PPI immobilized in this flow cell can be detected by surface plasmon resonance with high sensitivity.

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IN THE CLAIMS:

Please amend claim 1 as follows:

1. (AMENDED) A process for detecting or determining a C-peptide-containing impurity in a sample of recombinantly produced human insulin or a derivative thereof, by a non-radioactive assay, comprising the steps:

(a) preparing a sample of recombinantly produced human insulin or a derivative thereof;
(b) mixing the samples with dilution buffer;
(c) adding a tracer to mixture (b);
(d) adding antibody specific for the C-peptide impurity to mixture (c);
(e) adding a ["]C-peptide second antibody bead["] having at least one label to mixture (d); and
(f) detecting or determining the presence of the C-peptide-containing impurity.

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